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EDITORIAL

Identifying poor adherence to antihypertensive medications in patients with resistant hypertension

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Poor adherence (compliance) to antihypertensive medications is a major contributor to morbidity and mortality in patients with hypertension. Estimates in the literature of the extent of poor adherence in patients with hypertension vary between around 20% and 80%, so it is difficult to be sure of the proportion of patients affected. Good adherence to antihypertensive medications is important. In addition to achieving better blood pressure control and thus reducing adverse hypertension-related outcomes, good adherence prevents unnecessary treatment escalation, additional appointments, investigations for secondary causes and even potentially invasive interventions.

In a recent issue of *BJCP*, Avataneo *et al*. report a study that used therapeutic drug monitoring to define antihypertensive medication adherence profiles in patients with suspected resistant hypertension referred to a hypertension unit in Turin, Italy [1]. A liquid chromatography–tandem mass spectrometry approach was used to quantify a panel of ten different antihypertensive drugs in human plasma. Of the 50 patients considered to have apparent resistant hypertension who underwent therapeutic drug monitoring, 24% were found to be only partly adherent and 18% totally non-adherent to the antihypertensive medications they had been prescribed. The team also attempted to identify predictors of poor adherence and look at associations between self-reported adherence (albeit using a nonvalidated questionnaire), physician opinion of adherence and results of the therapeutic drug monitoring. No association was found with self-reported adherence, while physicians were often able to identify non-adherence. Interestingly, all nine patients found to be totally non-adherent according to results of therapeutic drug monitoring self-reported that they were fully adherent. Factors found to be associated with non-adherence included higher blood pressures, higher heart rate, previous coronary artery disease or stroke and previous invasive treatments including renal denervation and baroreceptor stimulation. The authors concluded that there was a high prevalence of poor adherence in this patient group and expressed the need for caution in use of invasive treatments in patients with resistant hypertension without first addressing adherence. They suggested that there was a need for validation of the use of therapeutic drug monitoring in a wider cohort of patients to inform whether it should become routine clinical practice.

This was a relatively small study and measured a relatively small panel of antihypertensive drugs, but it adds to our knowledge of the extent of non-adherence in this important group of patients with resistant hypertension and some of the possible predictors of non-adherence in such patients. Resistant hypertension is a difficult problem, and while recent clinical trials such as PATHWAY-2 have highlighted effective treatment options in this scenario [2], identifying which patients have *true* resistant hypertension is important before additional therapies or other interventions are

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introduced, and one of the key things to exclude is non-adherence to medications.

There have been previous studies also describing the measurement of drugs or biomarkers in urine or blood of patients with hypertension. These more objective methods of assessing adherence have become more popular and widely available in recent years. For example, in 2014, Tomaszewski *et al*. published a study that used high-performance liquid chromatography–tandem mass spectrometry urine analysis to screen for the 40 most commonly prescribed medications or their metabolites in spot urine samples of 208 hypertensive patients attending a specialist hypertension centre in Leicester, United Kingdom [3]. Twenty-five per cent of these patients were found to be totally or partially non-adherent to antihypertensive treatment. The highest prevalence of poor adherence was among 'follow-up' patients with inadequate blood pressure control and patients who at the time had been referred for consideration of renal denervation therapy. Another study using similar urine analysis techniques highlighted that in patients from the United Kingdom and the Czech Republic being screened for adherence due to suspicion of non-adherence, the more antihypertensive medications patients were prescribed, the more likely they were to be non-adherent. In that study, nearly 80% of the patients in the United Kingdom who were prescribed six or more antihypertensive medications were found to be non-adherent [4]. A Dutch *post hoc* analysis of nearly 100 patients with apparent resistant hypertension previously included in the SYMPATHY renal denervation randomized-controlled trial showed that, on testing of stored blood samples using liquid chromatography–tandem mass spectrometry, 68% of the patients were non-adherent [5]. Patients and clinicians were unaware that there would be an assessment of adherence at the time these samples were collected as ethical approval to perform this analysis on the stored samples was obtained retrospectively.

Measurement of drugs or biomarkers is just one way of assessing adherence. Different methods are available depending on the setting and the resource available. These alternatives range on a spectrum from the less accurate but relatively simple methods of asking the patient, patient diaries, basic adherence questionnaires and pill counts to the more accurate but more invasive or expensive methods of review of prescription or dispensing records, electronic monitoring devices such as 'smart containers' or directly observed therapy [6]. Measurement of drug or biomarkers in urine or plasma would be classed as one of the more invasive and expensive but objective methods.

Adherence to medication is a general marker of good health behaviour. A 2006 meta-analysis noted that good adherence to *placebo* was associated with a 44% lower mortality [7]. When we consider non-adherence, we often think about patients 'forgetting' to take their medication – so-called 'unintentional non-adherence'. However, 'intentional non-adherence' is probably much more common than we think. Some patients have a frank discussion with their clinician about the extent of their non-adherence and the reasons for it. However, we know that there are probably many more patients who choose not to disclose this or are perhaps not invited or encouraged enough to discuss it openly. There are also some patients who show 'white-coat adherence', starting to take their medications regularly just before each contact with a health care professional but taking them less regularly at other times. At the other extreme, 'over-adherence' can also be a problem with patients escalating doses higher than those recommended leading to adverse effects or taking additional medications not currently prescribed with the possibility of interactions. There is also the issue of 'pathological adherence', when patients persist with taking a medication that is causing them significant side effects without seeking help until their next routine follow-up appointment.

Identifying non-adherence is a good thing. It puts all the cards on the table and opens up an honest discussion between the patient and the clinician so that they may select an appropriate and realistic management plan that is acceptable to both. Educating the patient about hypertension and the benefits of treatment is important, as is building a good clinician–patient relationship. Ideally, we should ask every patient about adherence at every appointment. However, in the authors' opinions and clinical experience, and based on the literature around adherence [8], there are a few 'warning signals' that should prompt a more detailed consideration of adherence (Table 1). While attempts to measure and address adherence with patients' co-operation are important, we must also respect patients' autonomy to make their own decisions about whether to take medications or not.

It is clear from the Avataneo *et al*. study and others that patient self-reporting of adherence is unreliable. In addition, clinicians cannot always tell when poor adherence is a contributing factor to resistant hypertension. Therefore, more objective measures of adherence that can be applied during a routine consultation are welcome. In clinical care, the patient should of course be informed and give their consent to have any invasive measurement of adherence performed as part of the consultation. Several studies have

Table 1

'Warning signals' that should prompt a detailed consideration of adherence to antihypertensive medication

Patient expresses a lack of belief in benefits of antihypertensive treatment
Patient expresses concerns about adverse effects of medications
Patient expresses that they are tired of taking medications
Patient expresses a fear of lifelong treatment
Poor understanding of hypertension and the benefits of treatment
Unexpected increase in blood pressure
Inadequate response to treatment or 'resistant hypertension'
Complex treatment regimen or multiple co-morbidities
Poor attendance at planned review appointments
Communication difficulties
Previous unsatisfactory clinician encounters
Depression or other psychiatric illness
Significant competing priorities, e.g. caring responsibilities for other family members, financial issues (in some health care settings)
Poor social or family support network

now shown that techniques such as that described in the Avataneo *et al*. study can be applied effectively in various populations of patients with hypertension. In our opinion, these measurements are very likely to be cost-effective in the longer term, given the potential avoidance of years of unnecessary or unhelpful appointments and additional interventions once non-adherence is revealed and can be addressed. As availability of these measurement techniques improves, health services should embrace their use, at least in selected patients such as those with apparent resistant hypertension. Definitively identifying patients in whom adherence is an issue is the first step to improving their care in the future. The next steps involve successfully addressing non-adherence once identified while continuing to respect patients' autonomy. Already, behavioural interventions such as motivational interviewing show some promise in this area [9]. Further research into how best to act upon the results of drug monitoring to improve adherence and patient outcomes and how these efforts can effectively be incorporated into clinical care for patients with hypertension is required.

Competing Interests

I.S.M. is an Executive Editor of *BJCP* and a member of the British and Irish Hypertension Society Collaborative Research Working Party. T.M.M. is a member of the British and Irish Hypertension Society Collaborative Research Working Party.

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